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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,219	07/26/2000	Jeffrey Browning	A046 US	7978

959 7590 09/20/2004

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/626,219	BROWNING ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,24-26,31-33 and 36-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20, 24-26, 31-33, and 36-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on June 22 2004 is acknowledged.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20, 24-26, 31-33, and 36-53 are pending and under consideration.

Claim Rejections - 35 USC § 112, Maintained

Claims 20, 24-26, and 31-51 remain rejected and the new claims 52, and 53 are also under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are interpreted as drawn to method of treating follicular lymphoma by administering composition comprising a soluble lymphotoxin beta receptor to a subject (base claims 20 and 43), to a mammal (claim 24) or to a human (claims 25), wherein the dependent claims 26, 36, 44, and 45 describe what happen after said administrating said composition, wherein dependent claims 31-33 further comprises another known cancer therapy, wherein claims 37-42, and 46-51 further limits what other things could be attached to said soluble lymphotoxin beta receptor. The new base claim 52 is drawn to method of treating follicular lymphoma in a human by administering a pharmaceutical composition comprising a polypeptide that comprises a soluble, ligand-binding domain of human lymphotoxin beta receptor to the subject, wherein the soluble, ligand-binding domain of human lymphotoxin beta receptor comprises SEQ ID NO:1.

Applicant argues that the instant specification has working examples that demonstrate the efficacy of the soluble lymphotoxin beta receptor fused to human IgG Fc in treatment of SJL/RCS mice. The soluble lymphotoxin beta receptor fused to human IgG Fc results in lower tumor volume. The Examiner has inappropriately relied on references, which discuss the biological role of the soluble form of lymphotoxin (LT) within cultured cell lines and are not relevant to the use of a soluble form of LTPR in treating follicular lymphoma in a subject. Lymphotoxin as described in these publications (Higuchi et al., Qin et al., Wong et al., and Reisfeld et al.) refers to a secreted form, presently known as LT alpha, which binds to known TNF receptors. Appendix A, hereinafter referred to as the "Gommerman review" (Gommerman and Browning, Nature Reviews Immunology, 2003 J, 642) discloses that the distinction exists between signaling of soluble LT alpha and that of the LT alpha/beta heterodimer complex. Reliance on references to infer the effect of treatment with the soluble LT beta receptor of the instant invention is inappropriate. The Gommerman review teaches the unique signaling role of surface LT through LT beta receptor. Furthermore, the Gommerman review discusses the impact of the in vivo microenvironment on surface LT-LT beta receptor complex signaling, stating that surface LT expressed on the surface of some B cells functions to maintain FDCs (follicular dendritic cells) in a fully functional state, the loss of surface LT-LT beta receptor complex signaling in the splenic marginal zone results in the loss of various marginal-zone myeloid populations and marginal- zone B cells. Neither of these roles for surface LT-LT beta receptor complex signaling supports the Examiner's conclusion that inhibition of the LT signaling system,

as presently described in the art, would inherently lead to greater cell proliferation. Ponzio et al. teach the use of SJL mice to determine the effect of gamma- irradiation and cyclophosphamide administration on transplantation of spontaneous reticulum cell sarcomas (RCS). Administration of gamma- irradiation or cyclophosphamide to SJL mice was found to prevent transplantability of primary RCS, and to diminish the growth of established transplantable RCS lines. Thus, the conclusions of the Ponzio et al. reference are derived from studies of y- irradiated or cyclophosphnmide-treated SJL/RCS mice. In contrast, data presented in the instant specification describe treatment of SJL/RCS mice using soluble LT beta receptor and there is no reason for a skilled artisan to think that the administration of a soluble LT beta receptor (a much more targeted and subtle treatment than gamma- irradiation or cyclophosphamide) would have any inhibitory effect on transplantation per se. These arguments have been fully considered but found unpersuasive for following reasons.

The Office considered the data presented in the instant specification as well as what is known about the activity of a soluble lymphotoxin beta receptor in the art including applicant's numerous US patents and WIPO documents as well as other peer-reviewed journal articles.

US Patent 5, 925, 351 (one inventor common with the instant application) at Figure 2 (note the Figure legend at column 4 lines 63-65) teaches that a soluble lymphotoxin beta receptor inhibits LT-induced cell death. The '351 patent teaches at the abstract that a soluble lymphotoxin beta receptor binds to its ligand, lymphotoxin, thereby blocking LT signaling.

As for the lower LN weight observed for SJL/RCS mice who received the soluble lymphotoxin beta receptor, one in the art might look for explanation elsewhere because Ponzio et al (IDS, 1986, Intern. Rev. Immunol., vol. 1, pages 273-301) at page 288-291 teach unlike other tumor growth, immunosuppression have an adverse effect to transplantability of RCS. US Patent 5, 925, 351 at Fig. 5 and in the claims teaches a soluble lymphotoxin beta receptor results in immunosuppression. The Gommerman review (note this review was published 3 years after the instant application had been filed) at page 651, left column teaches that lymph-node microenvironment is still frontier at the time the review paper is published. The Gommerman review teaches that the administration of LT beta receptor –immunoglobulin fusion protein decreases the cellularity in Peyer's patches and can reduce marked expansion of T- and B-cell numbers in a lymph node.

Based on Ponzio et al., of record and the '351 patent of record, the Gommerman review, one would conclude that the lower LN weight SJL/RCS mice who received the soluble lymphotoxin beta receptor fusion protein might be due to the decreased cellularity in Peyer's patches and/or reduced T- and B-cell numbers in a lymph node. One skilled in the art would have questioned the efficacy of a soluble lymphotoxin beta receptor in treatment of lymphoma since the art as a whole teaches the cells in a lymph-node would decrease by administration of a soluble lymphotoxin beta receptor, leading to less weight of LN.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

LARRY R. HELMS, PH.D
PRIMARY EXAMINER